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19

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,134	10/10/2003	Hal S. Padgett	1328-005	1176

27860 7590 11/01/2007
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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/684,134	**Applicant(s)** PADGETT ET AL.	
	Examiner Amanda M. Shaw	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/15/2007.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-12,42 and 43* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1,2,4,5,7-12,42 and 43* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *8/15/2007*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed August 15, 2007. This action is made FINAL.

Claims 1-2, 4-5, 7-12, and 42-43 are currently pending. Claims 1, 7, 9, 10, 42 and 43 have been amended. Therefore Claims 1-2, 4-5, 7-12, and 42-43 will be addressed herein.

Withdrawn Objections

2. The objection made to the drawings in section 3 of the Office Action of March 12, 2007 is withdrawn in view of amendments made to the specification.

Withdrawn Rejections

3. The rejection made under 35 USC 112 2nd paragraph in section 4 of the Office Action of March 12, 2007 is withdrawn in view of amendments made to the claims.

The rejections over claims 1-2, 4, and 6-12 made under 35 USC 102(b) in section 5 of the Office Action of March 12, 2007 are withdrawn in view of amendments made to the claims.

The rejection made under 35 USC 103(a) in section 6 of the Office Action of March 12, 2007 is withdrawn in view of amendments made to the claims.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a new rejection necessitated by amendment:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the instant case the specification does not appear to provide support for the amendment which recites, "wherein said activity does not utilize the MutS/L/H enzyme system". The Applicants claim that support for this amendment is found in paragraph 180 wherein the instant method is distinguished from methods in which a heteroduplex is exposed to a cellular DNA repair system. Here the specification teaches that there is more than one mechanism available for mismatch repair in E. coli and states that one of the mechanisms for mismatch repair in E. Coli is the MutS/L/H enzyme system. It is unclear why the Applicants think that this teaching distinguishes the instant method from other methods in which a heteroduplex is exposed to a cellular repair system. Although the specification mentions the MutS.L/H enzyme system, it does not provide adequate support for a method which does not utilize the MutS/L/H enzyme system. Further the MPEP states in section 2173.05(i) that any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for an exclusion. Therefore in the instant case the specification does not appear to provide specific support for negative limitation present in the amended claims.

Claim Rejections - 35 USC § 112 2^nd^ paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a new rejection necessitated by amendment:

Claims 42-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42-43 are indefinite over the recitation of the phrase "wherein said activity does not utilize the MutS/L/H enzyme system, proofreading activity, and ligase activity". This phrase in considered indefinite because it is unclear if Applicants are trying to claim a method which does not utilize the MutS/L/H system but uses proofreading activity and ligase activity or if Applicants are trying to claim a method which does not use the MutS/L/H system, proofreading activity, and ligase activity.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnold et al (WO 99/29902) as evidenced by Pochart (Journal of Biological Chemistry 1997).

Regarding Claims 42 and 43 Arnold teaches a method comprising preparing a heteroduplex between two polynucleotide sequences which contain regions of similarity with each other but also have at least two mismatches (Page 9, lines 14-16 and Page10, lines 9-10). Further Arnold teaches one embodiment wherein the at least two mismatches are separated by at least one complementary nucleotide base pair (Page 34 lines 9-21). Arnold teaches a method further comprising exposing a heteroduplex to enzymes of a DNA repair system which results in DNA repair at bulges in the heteroduplexes due to DNA mismatching (Page 9 lines 22-24). Here the DNA repair system works by cleaving at least one polynucleotide strand in the heteroduplex at or near the mismatch site. The method of Arnold further comprises a step of exposing the heteroduplex to a replication system, that repairs unmatched pairings (Page 9, lines 18-19). The replication system works by replacing at least one nucleotide at or near the cleavage site. The DNA repair and replication systems of Arnold use an effective amount of mismatch directed strand cleavage activity wherein said activity does not utilize the MutS/L/H enzyme system. Specifically Arnold teaches that the DNA repair system can be obtained as extracts from yeast (page 17, lines 30-34). As evidenced by Pochart, yeast cells have five nuclear MutS homologs, namely MSH2, 3, 6, 4, and 5

(Abstract). It is noted that in the instant case the claims only require that the "MutS/L/H enzyme system" is not used, the limitation does not prevent the use of MutS/L/H homologs from being used. Arnold further teaches that the resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands (Page 9, lines 28-30). Thus the method of Arnold produces polynucleotides that are not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. Arnold further teaches that the method comprises screening or selecting the population of variants for a desired functional property (Page 9, lines 30-31).

With regard to all of the claims rejected over Arnold et al (WO 99/29902), to address the limitation, "wherein at least one polynucleotide strand is formed that has a nucleotide sequence not identical to either parent or the complementary sequences of either parent", it is a property of the method of Arnold that it would produce such sequences. For example if one parent had the sequence of AT*C*GCTAGC*A*C and the second parent had the sequence of TA*T*CGATCG*G*G and these two strands formed a heteroduplex and were exposed to a DNA repair enzymes, wherein the DNA repair process it typically effected on both component strands of a heteroduplex molecule and at any party mismatch is typically random as to which strand is repairs, then the first parent strand could potentially cleave at the position shown in bold AT**C**GCTAGCAC and the second parent strand could potentially cleave at the position shown in bold TATCGATCG**G**G. After replacing the nucleotides on each strand the first strand would have the sequence ATAGCTAGCAC and the second strand would have the sequence TATCGATCGTG.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a new rejection necessitated by amendment:

8. Claims 1-2, 4, and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al (WO 99/29902) in view of Mashal (Nature Genetics 1995).

Regarding Claim 1 Arnold teaches a method comprising preparing a heteroduplex between two polynucleotide sequences which contain regions of similarity with each other but also have at least two mismatches (Page 9, lines 14-16 and Page10, lines 9-10). Further Arnold teaches one embodiment wherein the at least two mismatches are separated by at least one complementary nucleotide base pair (Page 34 lines 9-21). The method of Arnold further comprises exposing the heteroduplex to the enzymes of a DNA repair system which results in DNA repair at bulges in the heteroduplexes due to DNA mismatching (Page 9 lines 22-24). Here the DNA repair system works by cleaving at least one polynucleotide strand in the heteroduplex at or near the mismatch site. The method of Arnold further comprises a step of exposing the heteroduplex to a replication system, that repairs unmatched pairings (Page 9, lines 18-19). Here the DNA replication system works by replacing at least one nucleotide at or near the cleavage site. Arnold further teaches that the resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands (Page 9, lines 28-30). Thus the method of Arnold produces polynucleotides that are not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides.

Arnold teaches that any suitable DNA repair system can be used (page 3, lines 6-7), however Arnold does not teach specifically teach a method wherein the DNA repair system that is used cleaves the heteroduplex within six nucleotides 3' of the mismatch site.

However Mashal teach a method of detecting mutations by cleavage of DNA heteroduplexes with bacteriophage resolvases, namely T4 endonuclease VII (Abstract). It is an inherent property of this enzyme that it cleaves heteroduplexes 3' and within 6 nucleotides form the site of a mismatch.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arnold by using the T4 endonuclease VII DNA repair system to cleave the heteroduplex containing mismatches as suggested by Mashal. Mashal teaches that there are several advantages of using T4 endonuclease VII. For example reaction conditions are identical for all DNA fragments, the enzyme can recognize all four classes of nucleotide mismatches, and for fragments less than 500 bp in size, the enzyme can be applied directly to products of a PCR reaction without further purification (page 182, column 1). Further the enzyme provides information regarding the location of the mutation. The enzyme appears to be feasible for DNA fragments at least at large as 940 bp and possibly larger. Both recognition and cleavage of the mismatch occur in a single step (Page 182, column 1). For these reasons one of skill in the art at the time of the invention would have been motivated to use T4 endonuclease VII for the detection of mutations in many different research applications including methods for preparing variant polynucleotides. Further it would have been obvious to use T4 endonuclease VII because the substitution of one DNA repair enzyme for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Regarding Claim 2, Arnold teaches a method wherein the polynucleotides forming a heteroduplex are circular (Page 13, lines 3-4). Regarding Claim 4, Arnold et al teach that the parent polynucleotides can encode variant forms of a plurality of genes constituting a multigene pathway (Page 11).

Regarding Claim 4 Arnold teaches that the parent polynucleotides can encode variant forms of a plurality of genes constituting a multigene pathway (Page 11, lines 13-14), therefore Arnold teaches a method wherein at least one heteroduplex contains a gene.

Regarding Claim 7 Arnold teaches a method comprising preparing at least two different heteroduplexes among at least three parent polynucleotides which contain regions of similarity with each other but also have at least two mismatches (Page 9, lines 14-16 and Page10, lines 9-10). Arnold specifically teaches that the number of parent polynucleotides to be combined can vary in size and range from two to 10 (page 10, lines 18-19), therefore if you are using 10 different parents then at least two different heteroduplexes would be formed. Further Arnold teaches one embodiment wherein the at least two mismatches are separated by at least one complementary nucleotide base pair (Page 34 lines 9-21). The method of Arnold further comprises exposing the heteroduplex to enzymes of a DNA repair system which results in DNA repair at bulges in the heteroduplexes due to mismatches (Page 9 lines 22-24). Here the DNA repair system works by cleaving at least one polynucleotide strand in the heteroduplex at or near the mismatch site. The method of Arnold further comprises a step of exposing the heteroduplex to a replication system, that repairs unmatched pairings (Page 9, lines 18-

19). Here the DNA replication system works by replacing at least one nucleotide at or near the cleavage site. Arnold further teaches that the resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands (Page 9, lines 28-30). Thus the method of Arnold produces polynucleotides that are not identical to any of at least three parent polynucleotides or the complementary sequences of the at least three polynucleotides.

Arnold teaches that any suitable DNA repair system can be used (page 3, lines 6-7), however Arnold does not teach specifically teach a method wherein the DNA repair system that is used cleaves the heteroduplex within six nucleotides 3' of the mismatch site.

However Mashal teach a method of detecting mutations by cleavage of DNA heteroduplexes with bacteriophage resolvases, namely T4 endonuclease VII (Abstract). It is a property of this enzyme that it cleaves heteroduplexes 3' and within 6 nucleotides form the site of a mismatch.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arnold by using the T4 endonuclease VII DNA repair system to cleave the heteroduplex containing mismatches as suggested by Mashal. Mashal teaches that there are several advantages of using T4 endonuclease VII. For example reaction conditions are identical for all DNA fragments, the enzyme can recognize all four classes of nucleotide mismatches, and for fragments less than 500 bp in size, the enzyme can be applied directly to products of a

PCR reaction without further purification (page 182, column 1). Further the enzyme provides information regarding the location of the mutation. The enzyme appears to be feasible for DNA fragments at least at large as 940 bp and possibly larger. Both recognition and cleavage of the mismatch occur in a single step (Page 182, column 1). For these reasons one of skill in the art at the time of the invention would have been motivated to use T4 endonuclease VII for the detection of mutations in many different research applications including methods for preparing variant polynucleotides. Further it would have been obvious to use T4 endonuclease VII because the substitution of one DNA repair enzyme for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Regarding Claim 8, Arnold teaches that the heteroduplex is exposed to a replication system which result in the production of a plurality of variant polynucleotides (Page 9, lines 18-19).

Regarding Claim 9 Arnold teaches a method comprising preparing a heteroduplex between two polynucleotide sequences which contain regions of similarity with each other but also have at least two mismatches (Page 9, lines 14-16 and Page10, lines 9-10). Further Arnold teaches one embodiment wherein the at least two mismatches are separated by at least one complementary nucleotide base pair (Page 34 lines 9-21). The method of Arnold further comprises exposing the heteroduplex to enzymes of a DNA repair system which results in DNA repair at bulges in the heteroduplexes due to DNA mismatching (Page 9 lines 22-24) Here the DNA repair system works by cleaving at least one polynucleotide strand in the heteroduplex at or near the mismatch site. The method of Arnold further comprises a step of exposing the heteroduplex to a replication system, that repairs unmatched pairings (Page 9, lines 18-19). Here the replication system works by replacing at least one nucleotide at or near the cleavage site. Arnold further teaches that the resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands (Page 9, lines 28-30). Thus the method of Arnold produces polynucleotides that are not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. Finally Arnold teaches a method also comprising screening or selecting the population of variants for a desired functional property (Page 9, lines 30-31).

Arnold teaches that any suitable DNA repair system can be used (page 3, lines 6-7), however Arnold does not teach specifically teach a method wherein the DNA repair system that is used cleaves the heteroduplex within six nucleotides 3' of the mismatch site.

However Mashal teach a method of detecting mutations by cleavage of DNA heteroduplexes with bacteriophage resolvases, namely T4 endonuclease VII (Abstract). It is a property of this enzyme that it cleaves heteroduplexes 3' and within 6 nucleotides form the site of a mismatch.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arnold by using the T4 endonuclease VII DNA repair system to cleave the heteroduplex containing mismatches as suggested by Mashal. Mashal teaches that there are several advantages of using T4 endonuclease VII. For example reaction conditions are identical for all DNA fragments, the enzyme can recognize all four classes of nucleotide mismatches, and for fragments less than 500 bp in size, the enzyme can be applied directly to products of a PCR reaction without further purification (page 182, column 1). Further the enzyme provides information regarding the location of the mutation. The enzyme appears to be feasible for DNA fragments at least at large as 940 bp and possibly larger. Both recognition and cleavage of the mismatch occur in a single step (Page 182, column 1). For these reasons one of skill in the art at the time of the invention would have been motivated to use T4 endonuclease VII for the detection of mutations in many different research applications including methods for preparing variant polynucleotides. Further it would have been obvious to use T4 endonuclease VII because the substitution of one DNA repair enzyme for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Regarding Claim 10 Arnold teach that a second heteroduplex comprising at least one variant strand can be formed and the process can be repeated. Specifically Arnold et al teach that the variants can be subjected to further rounds of recombination using the heteroduplex procedures (Page 18, lines 8-11).

Regarding Claims 11 and 12 Arnold et al teach that the variant polynucleotides can be converted to RNA and be translated prior to screening and selecting. Specifically Arnold et al teach that the variant polynucleotides (DNA) as well as their expression products or secondary metabolites produced by their expression products are isolated a screened for the desired property (Page 18, lines 13-15). In order for the expression products to analyzed, the DNA would have had to been converted to RNA and then translated.

With regard to all of the claims rejected over Arnold et al (WO 99/29902) in view of Mashal (Nature Genetics 1995), to address the limitation, "wherein at least one polynucleotide strand is formed that has a nucleotide sequence not identical to either parent or the complementary sequences of either parent", it is a property of the method of Arnold that it would produce such sequences. For example if one parent had the sequence of AT*C*GCTAGC*A*C and the second parent had the sequence of TA*T*CGATCG*G*G and these two strands formed a heteroduplex and were exposed to a DNA repair enzymes, wherein the DNA repair process it typically effected on both component strands of a heteroduplex molecule and at any party mismatch is typically random as to which strand is repairs, then the first parent strand could potentially cleave at the position shown in bold AT**C**GCTAGCAC and the second parent strand could potentially cleave at the position shown in bold TATCGATCG**G**G. After replacing the nucleotides on each strand the first strand would have the sequence ATAGCTAGCAC and the second strand would have the sequence TATCGATCGTG.

The following is a new rejection necessitated by amendment:

9. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold (WO 99/29902) in view of Mashal (Nature Genetics 1995) as applied to claims 1 and 4 above, and in further view of Wetmur (US Patent 5877280).

The teachings of Arnold and Mashal are presented above.

The combined references do not teach a method wherein the heteroduplex polynucleotide sequence is a genome.

However, Wetmur et al teaches a method called genome mismatch scanning. This method created for whole genome scanning utilizes E. coli MutS and the other enzymes of the mismatch repair system to detect differences between two strands of oligonucleotides (Column 12, lines 49-64).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Arnold et al to an entire genome. One would have been motivated to do so in order to detect differences between two genomes which can then be applied towards genome mapping and or cloning genes based on sequence differences or similarities between the two genomes (Column 12, lines 49-64).

Response To Arguments

10. In the response filed August 15, 2007, the Applicants have amended claims 1, 7, and 9 to require a step of "cleaving at least one polynucleotide strand in said heteroduplex within six nucleotides 3' of a mismatch site" in order to overcome the rejections made under 35 USC 102 (b). The Applicants argument and amendment have been fully considered and found persuasive. These claims are no longer rejected under 35 USC 102 (b) and a new rejection has been made under 35 USC 103 (a) (see above). Regarding Claims 42 and 43 the Applicants have amended claims 42 and 43 to

require "an effective amount of mismatch directed strand cleavage activity wherein said activity does not utilize the MutS/L/H enzyme system" in order to attempt to overcome the rejections made under 35 USC 102(b). The Applicants argument and amendment have been fully considered but are not found persuasive. The Applicants believe that the method of Arnold is thought to require exposing the heteroduplex to the MutS/L/H enzymes or their homologs to effect cleavage of the heteroduplex. While it is true that Arnold teaches that in vitro repair can be accomplished using the repair system of E. coli which uses MutS/L/H enzymes, Arnold also teaches that the repair system of yeast cells can be used. As evidenced by Pochart yeast cells have five nuclear MutS homologs, namely MSH2, 3, 6, 4, and 5 (Abstract). It is noted that in the instant case the claims only require that the "MutS/L/H enzyme system" is not used, the limitation does not prevent the use of MutS/L/H homologs from being used. Therefore the Arnold reference can still be applied.

Further the Applicants point to Examples 6 and 14 in the specification which deal with negative control reactions and conclude that based on these examples the method of Arnold does not anticipate the instant method. Additionally the Applicants have filed a declaration under 37 CFR 1.132 in which Dr Padgett reviews experiments performed in Examples 3, 4, 6, and 10 and concludes that using internal mismatch repair systems results in much less efficient recombination than the in vitro system of Cell, polymerase, and ligase, therefore Arnold does not anticipate the invention.

However, this is not considered persuasive since Dr. Padgett's arguments are not commensurate with the scope of the claims. First, Dr. Padgetts arguments are based on color drawings which were not received by the office. Further the arguments are based on the facts that the system consisting of Cell nuclease, polymerase and ligase only produced a larger number or recombinants and different recombinants from the in vivo repair system in E. coli. Even assuming that intact cells are equivalent to cell extracts, as argued by Applicants, the claims do not contain any specific limitation of the recombination frequency or the structure of the recombination products. Further the claims do not even require the use of Cell nuclease.

Finally with regard to the rejection made under 103(a), the Applicant's state that the secondary reference does not cure all of the deficiencies that Arnold fails to teach. The Applicants argument has been fully considered and in light of the amendments made to the claims the rejection made over Arnold in view of Wetmur has been withdrawn and a new rejection has been made under 35 USC 103 (a) (see above) over Arnold in view of Mashal and in further view of Wetmur.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

Juliet S
JULIET C. SWITZER
PRIMARY EXAMINER

JULIET C. SWITZER
ARY EXAMINER